

COMPLEXES OF NITRIC OXIDE WITH POLYAMINES

FIELD OF THE INVENTION

The present invention is concerned with providing stable complexes of nitric oxide with certain polyamines, which complexes are useful in treating cardiovascular disorders, including hypertension.

Related compounds with the same utility are described in Ser. No. 07/316,958, filed on Feb. 28, 1989, now U.S. Pat. No. 4,954,526; Ser. No. 07/409,552, filed on Sep. 15, 1989, and Ser. No. 07/423,279, filed on Oct. 18, 1989; all of which are incorporated by reference.

BACKGROUND OF THE INVENTION

Endothelium-derived relaxing factor (EDRF) is a labile humoral agent which is part of a cascade of interacting agents involved in the relaxation of vascular smooth muscle. EDRF is thus important in the control of vascular resistance to blood flow and in the control of blood pressure. Some vasodilators act by causing EDRF to be released from endothelial cells. (See Furchgott, *Ann. Rev. Pharmacol. Toxicol.* 24, 175-197, 1984). Recently, Palmer et al have shown that EDRF is identical to the simple molecule, nitric oxide, NO. (*Nature* 317, 524-526, 1987). It has been hypothesized for years that many nitrovasodilators that mimic the effect of EDRF, like glyceryl trinitrate, amyl nitrite, NaNO₂, and sodium nitroprusside (SNP), do so by virtue of their conversion to a common moiety, namely NO, which is also a vasodilator. (See Kruszyna et al, *Tox. & Appl. Pharmacol.* 91, 429-438, 1987; Ignarro, *FASEB J.* 3, 31-36, 1989; Ignarro et al, *J. Pharmacol. Exper. Therapeutics* 218 (3), 739-749, 1981).

Keefer et al, in U.S. Pat. No. 4,954,526, disclose a method of treating cardiovascular disorders in mammals by administering stabilized nitric oxide primary amine complexes to mammals in need thereof. U.S. Pat. No. 4,954,526 is expressly incorporated by reference.

Spermine is a polyamine (a molecule containing several amino functions) that by itself has been reported to show some hypotensive activity (Marmo, Berrino, Cazola, Filippelli, Cafaggi, Persico, Spadaro and Nistico, *Biomed. Biochim. Acta*, 1984, 43, 509-515).

Longhi et al, in *Inorganic Chemistry*, 1(3), 768-770 (1962), reported that their reaction of N,N'-dimethylethylenediamine with nitric oxide utilizing high pressure techniques produced the compound Me—N(N₂O₂⁻)—CH₂—CH₂—N(N₂O₂⁻)Me Me—NH₂+—CH₂—CH₂—NH₂+Me. Based upon preliminary studies made by the present inventors, Longhi et al may have instead produced a compound of the structure CH₃NH₂+CH₂CH₂N(N₂O₂⁻)CH₃. No uses are reported by Longhi et al for the compound prepared.

SUMMARY OF THE INVENTION

There is growing evidence that nitric oxide is released from the endothelial cells that line all blood vessels in the body during a key step in the normal relaxation of the underlying vascular smooth muscle and hence plays a crucial role in controlling blood pressure. Thus, one object of the present invention is to develop compounds which can, in a controlled manner, release nitric oxide in vivo.

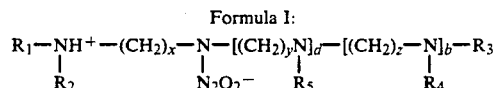
Another object of the present invention is to provide complexes of nitric oxide and polyamines, which complexes are unusually stable, long acting, and potent

cardiovascular agents when compared with prior known nitric oxide-amine complexes.

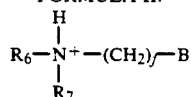
Still another object of the present invention is to provide methods of treating cardiovascular disorders using the stable and potent nitric oxide polyamine complexes herein disclosed, and to provide pharmaceutical compositions which contain such complexes.

Accordingly, the present invention provides the following Formulas I, II and III: nitric oxide-polyamine complexes and pharmaceutically acceptable salts thereof as useful cardiovascular agents.

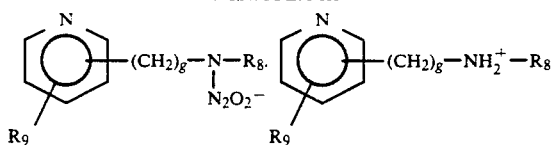
Formula I:



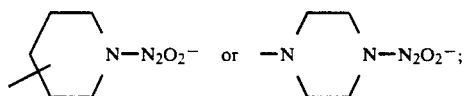
FORMULA II:



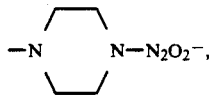
FORMULA III:



In the above Formulas I, II and III, b and d are independently zero or one; x, y and z are independently two to twelve; R₁ to R₈ are independently hydrogen, C₃₋₈ cycloalkyl, C₁₋₁₂ straight or branched chain alkyl, benzyl, benzoyl, phthaloyl, acetyl, trifluoroacetyl, p-toluy, t-butoxycarbonyl or 2,2,2-trichloro-t-butoxycarbonyl; R₉ is hydrogen or a C₁-C₁₂ straight or branched chain alkyl; B is



f is zero to twelve, with the proviso that when B is the substituted piperazine moiety



then f is two to twelve; and g is two to six. The group —N₂O₂⁻ has the structure



The compounds of Formulas I, II and III encompassed hereby, are thought novel with the exception of the Formula I compound, wherein R₁ and R₃ are methyl, R₂ is hydrogen, x is 2, and b and d are zero.

Preferred among the above compounds of Formulas I and II, are those compounds wherein R₁ to R₇ are independently hydrogen, C₃₋₈ cycloalkyl, C₁₋₁₂ straight or branched chain alkyl, benzyl or acetyl. More pre-